

## Polio to the rescue; New frontiers in glioblastoma treatment

Syed Sarmad Bukhari, Aneela Darbar, Muhammad Shahzad Shamim

### Abstract

Lack of substantial progress in effective treatment of glioblastoma multiforme has led investigators to explore unconventional treatment options including the use of tumour treating fields and oncolytic virotherapy. Herein the authors have reviewed some of the recent literature on oncolytic virotherapy for the treatment of glioblastoma multiforme.

**Keywords:** Glioblastoma, virotherapy, oncolytic, immunomodulation

### Introduction

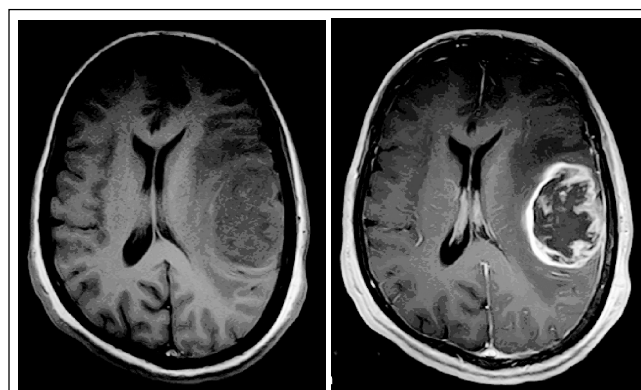
The year is 2005 and Temozolomide becomes the first major breakthrough to be allowed FDA approval for glioblastoma treatment with significant improvement in survival in the preceding two decades. This treatment saw an improvement in overall survival from a median of 6.9 months in 1995-96 to 10.3 months in those diagnosed between 2010-15 with 2-year survival peaking to 18%.<sup>1</sup> Several known and newly discovered chemotherapy agents have been tested with marginal or no improvement in overall survival.<sup>2</sup> A major field in glioblastoma research is immunomodulation. Amongst the many methods currently under review, using a pathogenic virus to stimulate the immune response into killing tumour cells holds significant promise.

### Review of evidence

The idea is neither new nor unique and is derived from fairly well established historical evidence of spontaneous tumour regression following immunization or incidental viral infection. For directed therapy, these viruses must infect only the target of interest, must not damage normal cells and be phased out of the host once its job is done.<sup>3</sup> Such a combination is hardly found in nature. Scientists therefore, have turned to genetic engineering for the task. Such viruses are known as oncolytic and the neurotropic poliovirus was considered for this purpose in the 1990s. The prototype oncolytic poliovirus, termed PVS-RIPO, is

The Aga Khan University Hospital, Karachi, Pakistan.

**Correspondence:** Muhammad Shahzad Shamim  
e-mail: shahzad.shamim@aku.edu



**Figure a) b)** MRI T1WI, axial sections, pre and post-contrast images show a heterogeneously enhancing mass lesion with central necrosis and intense perilesional oedema, characteristic radiological features of glioblastoma multiforme

the live attenuated poliovirus type 1 (Sabin) containing a heterologous IRES (internal ribosome entry site) derived of human rhinovirus type 2 (HRV2).<sup>4</sup> This chimera is capable of entering and lysing tumour cells but cannot infect or replicate in normal cells that are capable of triggering an immune response, which tumour cells cannot. Genetic stability was ensured following serial transmission through HeLa cell lines, which are one of the oldest and most commonly used cell lines.<sup>5</sup>

Preliminary studies in animals showed the virus to be effective in eliminating neuroblastoma and glioblastomas in mice to certain success. In these early studies, tumour inoculum would be placed in mice and allowed to grow followed by intra-tumoural injection of PVS-RIPO.<sup>6,7</sup> The results were very promising and shortly trials using human subjects were initiated by Gromeier and colleagues at Duke University. In a landmark paper published in 2018, they described phase II trials involving a direct intra-tumoural inoculation of PVS-RIPO. The study lasted from May 2012 to May 2017 and involved 61 patients with recurrent glioblastoma. These patients were consecutively chosen after a single recurrence of glioblastoma with a KPS of no less than 70, a contrast enhancing tumour volume greater than 1 cm<sup>3</sup> and less than 5.5 cm<sup>3</sup>. A single stereotactic biopsy was taken prior to placement of catheter to deliver PVS-RIPO into the tumour for genetic

analysis and confirmation. Inoculum volumes (3.25 ml) were administered with a pump and imaging was acquired 4 hours after administration and thereafter at regular intervals.<sup>8</sup>

Results of the trial were promising with overall survival plateauing at 21% at 24 months in the PVS-RIPO group while overall survival continued to decline in the historical group. This was favourable to outcomes following treatment with Nova-TTF.<sup>9</sup> This study also showed patients to have a durable radiographic response following infusion with tumour volumes diminishing over time. Further work is required to determine which genetic variant of glioblastoma is most amenable to this treatment as new data comes to light regarding the molecular and genetic heterogeneity of this elusive and fatal disease.<sup>10</sup>

### Conclusion

Based on current evidence, we strongly believe that oncolytic virus therapy has an evolving role in glioblastoma management. Current evidence points towards its likely benefit in significantly improving survival in recurrent disease but it may also have a role to play in newly diagnosed glioblastoma as a means of either primary therapy of volume reduction prior to surgery in order to convert unresectable disease into one that is amenable to surgery.

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